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LXXXVI. A NOTE ON THE INHIBITORY EFFECT OF MONOIODOACETIC ACID ON LACTIC ACID PRODUCTION BY CANCER TISSUE.

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Lundsgaard, in recent work [1930, 1] has shown that monoiodoacetic acid prevents the production of lactic acid in contracting muscle. Later [1930, 2] he found that, with concentrations of iodoacetic acid which completely inhibit glycolysis, the oxidising systems of yeast and muscle remain unimpaired. Warburg has shown that tumour cells derive a large part of their energy for growth from glycolysis. If this glycolysis of tumour could be inhibited by iodoacetic acid as is that of muscle, the growth of the tumour might be checked. Lundsgaard states that he is testing the effect of iodoacetic acid on the growth of tumours in mice by injecting it into the living animal. In order to see whether such inhibition of growth might be expected in tumours, we tried the effect of iodoacetic acid on glycolysis of tumours *in vitro*. So far as is known, the mechanism of glycolysis in tumours differs considerably from that in muscle, the tumour glycolysis appearing to be independent of hexosephosphate [Harrison and Mellanby, 1930]. Lundsgaard showed that in muscle under the influence of iodoacetic acid hexosephosphate is synthesised but not broken down. Since the production of lactic acid in the tumour cell appears to be independent of the breakdown of hexosephosphate, it seemed to us possible that iodoacetic acid might not produce the same inhibiting effect upon the lactic acid production by tumours as it produced upon that by muscle. The experiments given in the table show, however, that iodoacetic acid causes a large inhibition in the production of lactic acid by tumours *in vitro*. As yet we are unable to explain by what mechanism the iodoacetic acid causes such inhibition in tumour glycolysis.

Experiments *in vitro*.

Mouse carcinoma 63 was cut into thin slices, weighed and dropped into flasks containing 50 cc. bicarbonate Ringer's solution (brought to p_H 7·8 by passing through it a mixture of 5 % CO_2 and air), 5 cc. 9·6 % glucose (final concentration = 0·8 %), and 5 cc. either of water or of a neutralised solution of iodoacetic acid dissolved in 0·8 % NaCl. 30 cc. were then removed into a solution of trichloroacetic acid for the determination of the amount of lactic

acid already present[1]. The flasks were then stoppered and shaken for 3 hours at 37° and, after removal of proteins and carbohydrates, the lactic acid was estimated by the method of Friedemann, Cotonio and Shaffer [1927].

Table I. *Aerobic glycolysis of tumour tissue as affected by iodoacetic acid.*

		mg. lactic acid per g. dry weight tissue mg.
Exp. 1.	Control	39·1
	Iodoacetic acid 2 mg. in 30 cc.	14·5
Exp. 2.	Control	41·4
	Iodoacetic acid 4 mg. in 30 cc.	7·3
Exp. 3.	Control	34·6
	Iodoacetic acid 4 mg. in 30 cc.	1·0
Exp. 4.	Control	30·3
	Iodoacetic acid 1 mg. in 30 cc.	8·9
	„ 2 mg. in 30 cc.	5·6
	„ 4 mg. in 30 cc.	3·0

In Exp. 3, the tissue had been shaken for an hour in bicarbonate Ringer's solution and then put into fresh Ringer's solution with glucose and shaken with and without iodoacetic acid.

Experiments *in vivo*.

Several experiments were done in which iodoacetic acid was injected in a sublethal dose into mice bearing tumour 63. After a given time, the animals were killed and the glycolysis of the tumour compared with that of tumours from uninjected animals. In order to make the control as valid as possible, both the injected and uninjected animals bore tumours from the same inoculation. Since there is some variation in the glycolytic values of untreated cancerous tissues from different animals even when the tumours are produced from the same parent tumour, it is evident that only very large differences between the degree of glycolysis of the tumours of the injected and the uninjected animals would be significant. Glycolytic values from a number of tumours were compared to give the control figure. The glycolytic value of 5 tumours of the same generation ranged between 31 and 43 mg. lactic acid per g. of tissue, and an average value of 37 mg. was taken for the control figure. The animals were given a subcutaneous injection (on the side opposite the tumour) of 0·2 cc. of 1 % iodoacetic acid (previously neutralised) and were killed from 1 to 2 hours afterwards. Their tumours were removed, sliced and put into sugar-containing bicarbonate Ringer's solution, and the experiment was run as already described. Animals A and B, killed respectively 1 and 2 hours after injection of iodoacetic acid, appeared to be normal and showed no symptoms of iodoacetic acid poisoning. Animal C, on the other hand, was almost moribund when killed 2 hours after injection.

[1] In the figures given in the tables this amount of preformed lactic acid has already been subtracted from the values both for the control solutions and those containing iodoacetic acid.

Table II. *Aerobic glycolysis of tumour slices after injection of iodoacetic acid.*

	Lactic acid per g. dry weight tissue mg.
Animal A	48·8
Animal B	56·5
Animal C	12·9
Control	37·0

The figures for the tumour glycolysis of the injected animals are an average of three experiments done on each tumour.

These results, although varying considerably from the control, at least indicate that when the dose of iodoacetic acid is sublethal, there is no inhibitory effect upon lactic acid production of the tumour after a single injection, but when the dose causes acute symptoms of poisoning, the lactic acid production of the tumour is strongly inhibited.

Summary.

1. The aerobic production of lactic acid by tumour slices is inhibited by iodoacetic acid.

2. A few experiments, on mice, in which a single injection of iodoacetic acid was given, show that no inhibition of lactic acid production in tumour occurs provided that the dose is sublethal.

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